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Prognostic Factors in Superficial Adult Soft Tissue Sarcomas: Analysis of a Series of 105 Patients

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Background and Objectives: This study was undertaken to study the behavior of superficial soft tissue sarcomas (STS) and determine the factors related to prognosis.

Methods: The clinical records of 105 adults (56 men, 49 women, mean age: 56.4 years) were retrospectively analyzed. Univariate analysis was performed on the entire group for overall survival (OS), and metastasis-free survival (MFS). Local recurrence-free survival (LRFS) was studied only on patients first treated in our institute.

Results: With a median follow-up of 111.9 months, 66 (62.9%) patients were alive; 25 (23.8%) had died of their disease. For the entire series, 10-year OS and MFS were 62.5% and 71.9% respectively. For fifty-two patients treated for their sarcoma at the Institution since the first tumor occurrence event, 10-year LRFS was 80%. Tumor grade was the only factor correlated with OS and MFS, while tumor size was the main factor correlated with LRFS.

Conclusion: Tumor size affects local control in STS while tumor grade is correlated with OS and MFS.

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KEY WORDS: **sarcoma; soft tissue; adult; prognostic factors; tumor grade**

INTRODUCTION

Adult soft-tissue sarcomas (STS) are rare tumors (0.7% of all adult malignancies) that occur in the extra-skeletal connective tissue [1]. They represent a heterogeneous group of tumors and are classified histologically according to their presumed histogenesis. To date, more than 60 types and subtypes have been identified [2]. Among tumor characteristics, tumor size and grade are two major prognostic factors of localized STS and form the basis of the AJC/UICC classification [3]. The importance of tumor depth has been stressed by Hajdu [4] and this has been recently confirmed [5–9]. Tumor depth is indeed in two large series an independent prognostic factor for tumor mortality and metastasis-free survival [5,7]. Superficial STS, defined as sarcoma developed above the fascia superficialis, are therefore reported as of better prognosis. However, the specific natural history of superficial sarcomas rarely has been considered.

This review of 105 superficial STS patients seen between 1967 and 1991 at Institute Bergonié was done in order to study the evolution and prognostic factors of this peculiar entity.

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MATERIALS AND METHODS

Patient Selection

From 1967 to 1991, 520 adult patients with soft-tissue sarcomas were treated at our institute, among whom 105 had superficial STS. Fifty-two patients were referred for the first treatment of their tumor, and 53 following one or several local treatments (surgery and/or radiotherapy) performed elsewhere.

For all patients considered in the study, histologic sections were reexamined by a pathologist (J.M.C.) at our institute, including all slides corresponding to biopsies or resections performed elsewhere. Immunohistochemical studies were used as needed to confirm the diagnosis and establish tumor type. Grade was assessed according to the grading system of the Fédération Française des Centres de Lutte Contre le Cancer (FNCLCC) based on the score obtained by evaluating tumor differentiation, necrosis, and mitotic count [10,11].

The following data were sought in each case: patient characteristics (sex and age and history at diagnosis), tumor characteristics (initial site, size, multifocal nature, pathologic data, grade, nodal involvement), treatment regimens (surgical procedures and results, radiotherapy), and evolution (data of first local recurrence and/or first metastases, general status at final visit). For referred patients, these data were sought from the referring clinician.

We checked that all patients included, especially those referred for a recurrence, really had a superficial STS by systemically reexamining all initial records, surgical reports (reassessed by ES), and histologic details.

Patients

This series included 56 men and 49 women aged 16 to 80 years (mean age, 56.4). Eleven patients had a history of previous cancer; localizations were: breast (four), skin (two), uterine cervix (one), testicle (one), chronic lymphoid leukaemia (one), retinoblastoma (one), and melanoma (one). Of these 11 patients, 8 received radiotherapy and 5 developed their sarcoma within the radiation field after a period ranging from 6 to 23 years (mean: 16.8). Moreover, one patient developed a radiation-induced sarcoma after radiotherapy of the scalp for tinea capitis during childhood. Two of the patients with breast cancer history had angiosarcoma on a lymphoedema of the upper limb (Stewart-Treves syndrome).

Locations of sarcoma were as follows: head and neck, 17; upper limbs, 23; lower limbs, 36; thoracic and abdominal wall, including groin, buttocks, and perineum, 29. Thus, in 59/105 (56.2%) cases the primary tumor was located on the extremities. Data on tumor size were available in 94 cases; initial size ranged from 1 to 15 cm, with a median size of 3 cm. Initial tumor size was <5 cm in 69 patients. Histological diagnosis are shown in Table I; malignant fibrohistiocytoma and leiomyosarcomas were the most frequent tumor types. Twenty-seven patients had grade 1 tumors, 53 grade 2 tumors, and 24 grade 3 tumors; grade was not assessable in 1 case.

TABLE I. Tumor Types of a Series of 105 Soft-Tissue Sarcomas Treated From 1967 to 1991 at the Institut Bergonié, Regional Cancer Center, Bordeaux, France

Malignant fibrous histiocytoma	39
Leiomyosarcoma	20
Dermatofibrosarcoma Protuberans	8
Fibrosarcoma	5
Unclassified sarcoma	5
Angiosarcoma	5
Malignant peripheral nerve sheath tumor	5
Atypical fibroaxanthoma	3
Liposarcoma	3
Synovial sarcoma	3
Extraskeletal osteosarcoma	3
Epithelioid sarcoma	2
Rhabdomyosarcoma	2
Alveolar soft-part sarcoma	1
Neuroepithelioma	1
Total	105

Treatment

Patients treated elsewhere and followed up. For five patients treated elsewhere, surgery was considered as already adequate at review, and patients were simply followed-up. In four cases, the treatment was wide resection of the tumor and biopsy scars, the margins being several centimeters of macroscopically healthy tissue. In one of these, radiotherapy (50 Gy) was also administered. In the later case, tumor-free margin could not be ascertained at a limited part of the tumor periphery, leading to additional radiotherapy (50 Gy plus 10 Gy boost to tumor bed). Complete remission was obtained in these five patients.

Other patients. For the other 100 patients, 52/100 patients were entirely treated at our institute since their first diagnosis, and 48/100 were referred after a first treatment elsewhere, either to complete the first treatment or because of a tumor recurrence. For those patients with initial care done elsewhere, the mean interval between diagnosis and referral to this institute was 28 months (range: less than 1 to 196 months). The different local treatments given are shown in Table II. None of these patients had received chemotherapy before being referred.

In 10/100 patients (9 already treated elsewhere and 1 seen for a first tumor occurrence), the treatment could only be palliative owing to metastatic spread ($n = 7$) and/or the site and extension of their local recurrences ($n = 3$). In none of these patients could a complete remission be obtained.

Eighty-nine of 100 other patients underwent surgery, and 1 was treated with intra-arterial chemotherapy followed by radiotherapy. Wide resection was possible in

TABLE II. Patients (n = 53) Referred After One or More Local Treatments Performed Elsewhere

	Surgery	Radiotherapy[a]
Only one therapeutic sequence		
Marginal resection only	27	3
Wide resection	9	1
Amputation	1	
Two therapeutic sequences		
Two marginal resections	6	2
One marginal resection + wide resection	3	
Three therapeutic sequences		
Three marginal resections	2	
Marginal resections with at least one wide resection	3	1
Four therapeutic sequences		
Marginal resections only	1	1
One marginal resection + three wide resections	1	
Total	53	8

[a]After examination of records, fields were considered adequate in only three cases. Minimal dose received was 50 Gy, except for 40 Gy in one patient.

76/89 cases, 43 of these treated with first intention and 33 for a recurrence. In 13/89 patients only marginal resection could be performed, with microscopic tumor foci less than 1 cm from the periphery of the resection specimen. A reconstructive procedure was needed in 26/89 cases (29.2%).

Postoperative complications affected 26/89 patients (29.2%) with scar disunion or necrosis (n = 24), infection (n = 1), or hemorrhage (n = 1). Only nine were severe enough to require a corrective surgical procedure. There were no surgery-related deaths.

Radiotherapy

The irradiated fields were planned according to results of the preoperative workup, surgical reports, and histological findings. In all cases, the field included the tumor bed and all tissues handled during intervention such as scars and drain courses; to this volume was added margins of 5 cm on all sides. The dose delivered was 50 Gy given in 25 fractions over 5 weeks with an eventual 10-Gy boost restricted to the tumor bed. CO^{60} photons, high-energy photons and electrons were used, alone or in combination.

Postoperative external beam radiotherapy was performed for 47 patients, including the 13 patients for whom only marginal resection could be obtained. The other irradiated cases were 34 patients with a wide surgical margin but with a tumor size over 5 cm or a tumor recurrence involving or encompassing the superficial aponeurosis.

Chemotherapy

Ten patients (five in each group) with high-grade tumors (grade 3) received chemotherapy either as primary (neoadjuvant n = 3) or adjuvant chemotherapy (n = 7) according to the policy at this institution at the time of their inclusion. Moreover, one patient received intra-arterial chemotherapy before radiotherapy.

Follow-Up and Statistical Analysis

Follow-up consisted of clinical examination with chest X-rays every 2 months for 2 years, then every 4 months for 3 years, and once a year afterward. Other tests (e.g., CT scan) were performed as needed. Local recurrences and/or metastases were documented by biopsies or unequivocal radiographic results. Overall survival (OS), local recurrence-free survival (LRFS), and metastasis-free survival (MFS) were calculated by the Kaplan-Meier method [12] from the date of initial diagnosis. Death from any cause was considered as an event of concern regarding OS.

Analysis for overall survival was done on the entire group (105 patients) after a separate analysis that showed no statistically significant difference in overall survival between patients treated since their first diagnosis at our institute (52 patients) and the others (53 patients), with 5-year overall survival of 84.5% and 68.1%, respectively ($P = 0.098$).

Analysis for metastasis-free survival was also done on the entire group because there was no statistically significant difference in MFS between patients treated since their first diagnosis at our institute and those referred for a local recurrence (n = 36), with 5-year metastasis-free survival of 89.2% and 69.1%, respectively ($P = 0.09$). Therefore, patients referred for a local recurrence were kept in the metastasis-free survival analysis.

Only the group of 52 patients treated at the Institute since the first occurrence of their disease was considered for LRFS calculations. For univariate analysis, the log-rank test [13] was used when two modalities of a variable were compared and a test for trend [14] was done when three modalities were considered. Variables were analysed for the following endpoints: OS, local recurrence, and metastatic relapse. P values of 0.05 or less were considered as statistically significant for prognostic factors.

RESULTS

The median follow-up at analysis was 111.9 months (range: 19.2–321.9 months). At the last follow-up visit, 66/105 (62.9%) patients were alive and tumor-free; 1 was alive with metastatic sarcoma and 1 was alive with another cancer. Ten of 105 patients (9.5%) died from a cause unrelated to the treated sarcoma; 25 (23.8%) deaths were related to sarcoma. Two patients were lost to follow-up: one after 4 years of event-free follow-up and the other with a local recurrence.

Following their management at the institute, 95/105

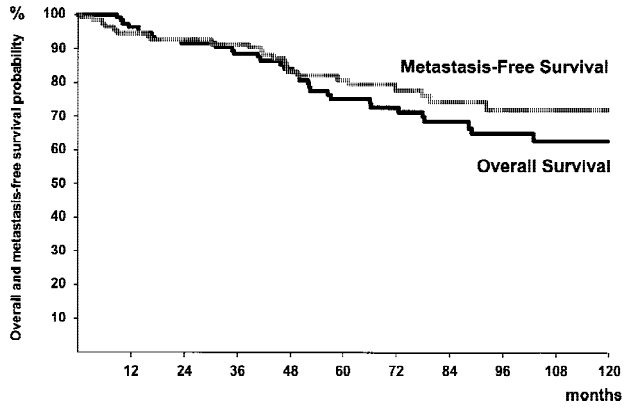

Fig. 1. Overall and metastasis-free survival of a series of 105 patients with superficial soft-tissue sarcomas. Institut Bergonié, Regional Cancer Center, 1967 to 1991.

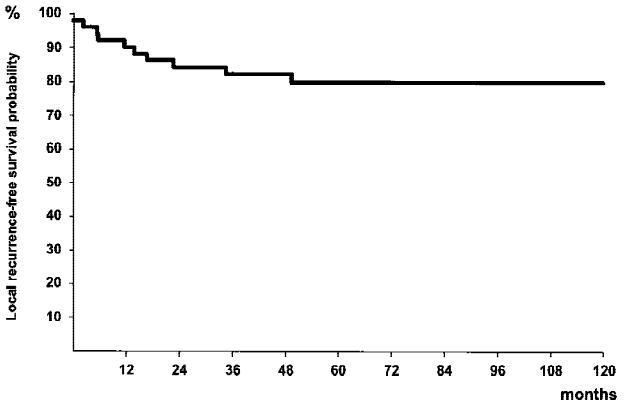

Fig. 2. Local recurrence-free survival of 52 patients with superficial soft-tissue sarcomas treated in Institut Bergonié since the first occurrence of their tumor, 1967 to 1991.

patients were free of disease. During their evolution, 11 patients presented a local recurrence after a median time of 16 months (range, 5–45 months). A new disease-free status was obtained for six of them, who were alive with no evidence of disease (follow-up: 36–128 months). The others died of their sarcoma. Fourteen patients had a metastatic relapse, associated with a local recurrence in two cases; all died except one, who is alive but with metastatic disease. Distribution of the 13 local recurrences observed according to local treatment strategy was as follows: 1/13 after marginal resection and 5/42 after wide surgery alone, 6/34 after wide surgery and radiotherapy; the only patient treated with intra-arterial chemotherapy followed by radiotherapy also recurred.

For the entire series, overall actuarial survival at 5 and 10 years was 75% and 62.5%, respectively, (Fig. 1). MFS at 5 and 10 years was 80% and 71.9% (Fig. 1). For those entirely treated at the institute, local recurrence-free survival was 80% at both 5 and 10 years (Fig. 2); no local recurrence was observed beyond 5 years of follow-up.

The univariate analysis of prognostic factors is summarized in Tables III and IV. Age and gender did not affect tumor evolution, although there was a better LRFS among men treated at the Institute ($P = 0.03$). Tumor site (extremities versus nonextremities) affected neither OS or MFS for the entire group, nor LRFS for patients treated in our institute since the first occurrence of their tumor ($P = 0.1$). Tumor size did not correlate with OS or MFS. However, patients with a tumor ≥5 cm had a significantly higher risk of local relapse ($P = 0.0006$; Fig. 3). Tumor grade was strongly correlated with OS ($P < 0.0001$; Fig. 4) and with MFS ($P < 0.0001$; Fig. 5). However, it did not affect LRFS ($P = 0.29$).

Finally, considering the extent of surgery in patients treated at our institute since their first tumor occurrence, type of surgery (wide resection versus marginal resection) did not affect risk of local recurrence ($P = 0.24$). However, all patients with a marginal tumor margin received postoperative radiotherapy.

TABLE III. Univariate Analysis for Prognostic Factors in Overall Survival and Metastasis-Free Survival of 105 Patients With Superficial Soft-Tissue Sarcomas, 1967–1991*

Factors		Number of patients	Overall 5- and 10-year survival rate		*P*	Metastasis-free 5- and 10-year survival rate		*P*
Age	≤50 year	46	86.2%	68.3%	0.1	81.9%	70%	0.99
	>50 year	59	65.3%	57.3%		79.3%	72.3%	
Sex	Male	56	74.7%	67%	0.8	78.5%	70.7%	0.82
	Female	49	75.7%	58.4%		83.5%	73.2%	
Tumor size[a]	<5 cm	69	79.5%	68.6%	0.18	79.7%	72.8%	0.71
	≥5 cm	25	59.4%	52%		87.7%	77.9%	
Location	Extremities	59	82.2%	68%	0.16	79.7%	71.3%	0.79
	Nonextremities	46	64.9%	55%		82.1%	72.4%	
Grade (FNCLCC)[b]	Grade 1	27	95.7%	95.7%		95.8%	95.8%	
	Grade 2	53	76%	58.2%	<0.0001	86.3%	71.4%	<0.0001
	Grade 3	24	47.4%	34.5%		49.4%	43.2%	

*FNCLCC = Fédération Nationale des Centres de Lutte Contre le Cancer. *P* values ≤ 0.05 were considered as statistically significant.
[a]In 11 cases tumor size was not assessable.
[b]In one case tumor grade was not assessable.

TABLE IV. Univariate Analysis for Prognostic Factors in Local Recurrence-Free Survival in Superficial Soft-Tissue Sarcomas, Institut Bergonié, Regional Cancer Center, 1967–1991*

Factors		Number of patients	Local recurrence-free 5- and 10-year survival rate		*P*
Age	≤50 year	21	85.2%	85.2%	0.44
	>50 year	31	76%	76%	
Sex	Male	26	91.1%	91.1%	0.03
	Female	26	68.3%	68.3%	
Tumor size[a]	<5 cm	37	91.7%	91.7%	0.0006
	≥5 cm	14	49%	49%	
Location	Extremities	27	88.9%	88.9%	0.1
	Nonextremities	25	69.8%	69.8%	
Grade (FNCLCC)	Grade 1	18	88.9%	88.9%	
	Grade 2	20	79.1%	79.1%	0.29
	Grade 3	14	71.4%	71.4%	
Resection	Wide	43	85.6%	85.6%	0.24
	Marginal	9	64.8%	64.8%	

*FNCLCC = Fédération Nationale des Centres de Lutte Contre le Cancer. *P* values ≤ 0.05 were considered as statistically significant.
[a]In one case tumor size was not assessable.

DISCUSSION

This study confirms that among soft-tissue sarcomas, superficial tumors represent a peculiar category with behavioral difference mainly characterized by a reduced metastatic risk. The 105 patients in this study represent 20.2% of the 520 STS patients treated at the institute during the time period under study. In this series, 59/105 (56.2%) superficial tumors were located on limbs, 29/105 (27.6%) on the trunk, and 17/105 (16.2%) on the head or neck. This topography is similar to that observed in deeply seated STS [1]. Moreover, there was no difference in sex ratio or age.

An important difference among the characteristics of superficial sarcomas is the lower incidence of high-grade disease; in this series 24/105 (22.9%) were grade 3 as compared to 40.5% in all STS patients taken together [7]. In the FNCLCC sarcoma group study, a strong correlation was found between deeper situation and higher grade. Because tumor grade also appears in this series to be the main prognostic factor for superficial tumor, the lower incidence of high-grade lesions can explain for a large part the better prognosis of superficial sarcoma.

Another explanation for this is the smaller size of superficial tumors. The median size in this series was 3 cm, and only 26.6% (25/94) of the tumors were 5 cm or more in diameter. This is to be compared with the median size of 7.0 cm found in a study concerning all operable sarcomas [7]. Moreover, size and depth are independent prognostic factors [6,7,9]. In our series of superficial tumors, difference in overall survival according to tumor size was not apparent, probably because of the low number of patients with large lesions.

Tumor size was, however, significantly correlated (*P* = 0.0006) with local outcome, with 5-year local recurrence-free survival of 91.7% and 49% for patients with

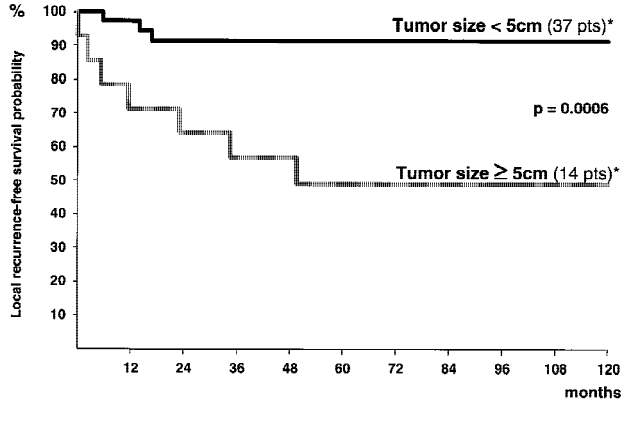

Fig. 3. Local recurrence-free survival according to tumor size of 52 patients with superficial soft-tissue sarcomas treated in Institut Bergonié since the first occurrence of their tumor, 1967 to 1991. Tumor size affects LRFS (*P* = 0.0006). Asterisk denotes tumor size not assessable in one case.

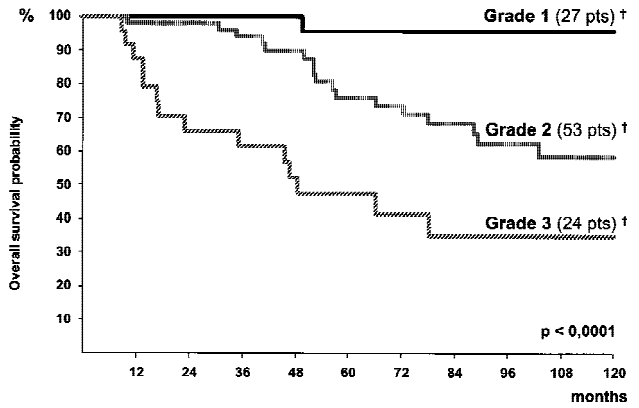

Fig. 4. Overall survival according to tumor grade (FNCLCC grading score) in a series of 105 patients with superficial soft tissue sarcomas. Tumor grade affects significantly overall survival (*P* < 0.0001). Cross denotes tumor grade not assessable in one case.

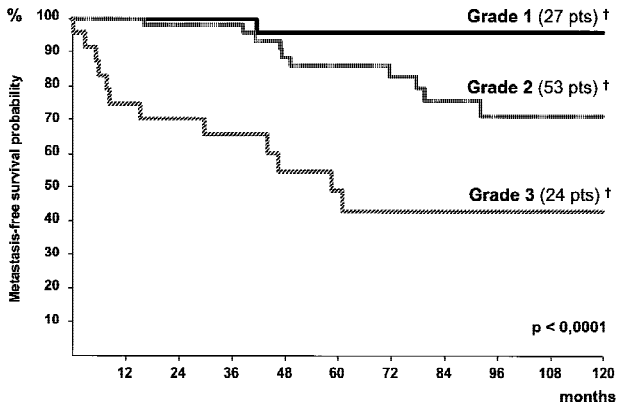

Fig. 5. Metastasis-free survival according to tumor grade (FNCLCC grading score) in a series of 105 patients with superficial soft-tissue sarcomas. Metastasis-free survival is significantly correlated with tumor grade ($P < 0.0001$). Cross denotes tumor grade not assessable in one case.

lesions of <5 cm and ≥5 cm, respectively (Table IV). Moreover, this difference appeared despite a reinforcement of local treatment, as radiotherapy was done in most of the patients with larger tumors.

As regards to local prognosis of soft-tissue sarcomas, quality of initial resection has been found to be an important prognostic factor for local control [5,6,9,15–21]. This was not significantly evidenced in the present series. However, analysis was done only on patients entirely treated at our institute, and only 8/52 of them had marginal resection and 7 of these 8 received postoperative irradiation. More than half of the present series was referred for a tumor recurrence. Consequences of local recurrence on the advent of metastases and survival is still debated [6]. It is to be noted that 17 patients were referred for a recurrence with evidence of superficial aponeurosis involvement or encompassement. This event is possibly significant as concern the general evolution of the disease. This hypothesis is to be tested by the study of a larger series with adequate follow-up since the first treatment. Therefore, adequate surgery should be considered as essential in the treatment of superficial sarcoma; this includes wide resection encompassing the superficial aponeurosis and 3 to 5 cm of normal tissue on all sides [22]. Postoperative radiation therapy is not necessary for most patients with correct surgery [23].

CONCLUSION

Tumor size appears to be the most important factor for local control. Tumor grade crucially affects metastatic risk and overall survival like in other series in which deep sarcomas were included [5,7]. Grade 3 superficial soft-tissue sarcomas should be considered for systemic treatment in prospective randomized trials.

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